

What is claimed is:

1. A method for suppressing or preventing rejection of a transplant in a patient, comprising administering to said patient an efficacious amount of a substance that inhibits SHIP  
5 function.
2. The method of Claim 1 in which said transplant is a bone marrow allograft, a solid organ allograft or xenotransplant, or an MHC disparate marrow graft having an MHC disparity of 1, 2, 3 or more allelic mismatches.
3. The method of Claim 1 in which said substance comprises a genetic construct.
- 10 4. The method of Claim 3 in which the genetic construct directs expression of an antagonist of SHIP function
5. The method of Claim 4 in which the genetic construct comprises an anti-sense polynucleotide, a polynucleotide that bind to SHIP mRNA, a nucleic acid that hybridizes to a SHIP mRNA, a recombinant retroviral vector, a ribozyme, an RNA aptamer, a  
15 peptidomimetic inhibitors of SHIP function, or a combination thereof.
6. The method of Claim 1 in which said substance is a small molecule inhibitor of SHIP activity having a molecular weight of less than about 10,000.
7. The method of Claim 1 in which said patient has cancer, autoimmune disease, HIV/AIDS, a genetic deficiency, or a combination thereof.
- 20 8. The method of Claim 1 in which said patient is in need of a histo-incompatible organ transplant, and further comprising the step of administering to said patient an allogeneic bone marrow transplant.
9. A method for treating or preventing graft-versus-host disease in a patient having or in need of a transplant, comprising administering to said patient an efficacious amount of a  
25 substance that inhibits SHIP function, in a pharmaceutically acceptable carrier.
10. The method of Claim 9 in which said transplant is a bone marrow allograft, a solid organ allograft or xenotransplant, or a MHC disparate marrow graft having an MHC disparity of 1, 2, 3 or more allelic mismatches.
11. The method of Claim 9 in which the substance comprises a genetic construct.
- 30 12. The method of Claim 11 in which the genetic construct directs expression of an antagonist of SHIP function.
13. The method of Claim 12, in which the genetic construct comprises an anti-sense polynucleotide, a polynucleotide that bind to SHIP mRNA, a nucleic acid that hybridizes

to a SHIP mRNA, a recombinant retroviral vector, a ribozyme, an RNA aptamer, and a peptidomimetic inhibitors of SHIP function, or a combination thereof.

14. The method of Claim 9 in which said substance is a small molecule inhibitor of SHIP activity having a molecular weight of less than about 10,000.

5 15. The method of Claim 9 in which said patient has cancer, autoimmune disease, HIV/AIDS, a genetic deficiency, or a combination thereof.

16. A therapeutic composition comprising a substance that inhibits SHIP function, in a pharmaceutically acceptable carrier.

17. A method for screening a substance suspected of inhibiting SHIP function, comprising:

10 providing a cell line that comprises an indicator of SHIP function;  
contacting the cell line with said substance; and  
measuring the response of said indicator to said substance,  
whereby the effectiveness of said substance as an inhibitor of SHIP function is  
assessed from the response of said indicator.

15 18. The method of Claim 17, in which the cell line is a NK cell line.

19. The method of Claim 17 in which the indicator is a fluorogenic substrate of SHIP.

20. The method of Claim 17 in which the response of said indicator is measured by flow cytometry or by a multi-well fluorescence detector.

20 21. The method of Claim 17 in which said indicator indicates Ly49 receptors, KIR, Fas, Fas ligand, or phosphatidyl serine in the extracellular leaflet of the plasma membrane.

22. The method of Claim 18, in which the substance comprises a small molecule inhibitor of SHIP activity, an anti-sense oligonucleotides, a peptidomimetic inhibitor of SHIP function, a ribozymes, nucleic acid, a polynucleotide, naked DNA, a recombinant retroviral vector, an RNA aptamer, an anti-sense oligonucleotide, or a combination  
25 thereof.

23. The method of Claim 22, in which said small molecule inhibitor is a suicide substrate for SHIP.

24. A method for screening a candidate genetic construct for inhibiting SHIP function, comprising:

30 providing an NK cell line that comprises an indicator of SHIP function;  
contacting said cell line with said genetic construct; and  
measuring the response of said indicator to said genetic construct,  
whereby the effectiveness of said genetic construct as an inhibitor of SHIP function is  
assessed from the response of said indicator.

25. A method for screening a substance suspected of inhibiting SHIP function, comprising:

(1) allowing SHIP to react with a SHIP substrate in the presence the substance, and taking a first measurement of a signal that indicates the extent of the SHIP/substrate reaction;

5 (2) allowing SHIP to react with a SHIP substrate in the absence the substance, and taking a second measurement of the same signal that indicates the extent of the SHIP/substrate reaction; and

(3) comparing the first and the second measurements, whereby a substance that inhibits SHIP function is selected.

10 26. The method according to Claim 25, wherein the SHIP substrate is selected from the group consisting of Shc, Grb2, the FcRIIB Receptor, PIP3, and IP4, or a modification thereof.\

27. The method of Claim 25, wherein the signal is a change in fluorescence intensity or in fluorescence spectra of the Substrate.

15 28. The method of Claim 25, wherein the substance is selected from a small molecule inhibitor of SHIP activity, an oligonucleotide, a peptidomimetic inhibitor of SHIP function, a ribozymes, a polynucleotide, a polypeptide, an anti-SHIP antibody, and an RNA aptamer.

29. The method of Claim 28, wherein the small molecule inhibitor of SHIP activity is a suicide substrate for SHIP.

20 30. A mouse cell comprising a SHIP<sup>fllox</sup> allele of a SHIP gene, which SHIP gene includes a first exon and a promoter, wherein at least the first exon and the promoter have been deleted in the SHIP<sup>fllox</sup> allele.

31. The mouse cell of Claim 30 wherein the cell is homozygous with regard to the SHIP<sup>fllox</sup> allele.

25 32. The cell of Claim 31, wherein the cell is an embryonic stem cell.

33. A transgenic mouse comprising a cell of Claim 31.

34. A mouse embryo comprising one or more stem cells of Claim 32.

35. A transgenic mouse derived from the embryo of Claim 34.

36. The transgenic mouse of Claim 33, wherein the mouse has a genotype of SHIP<sup>-/-</sup>.

30 37. The transgenic mouse of Claim 35, wherein the mouse does not express SHIP protein.